Radioactive Coronary Stents for the Prevention of Restenosis

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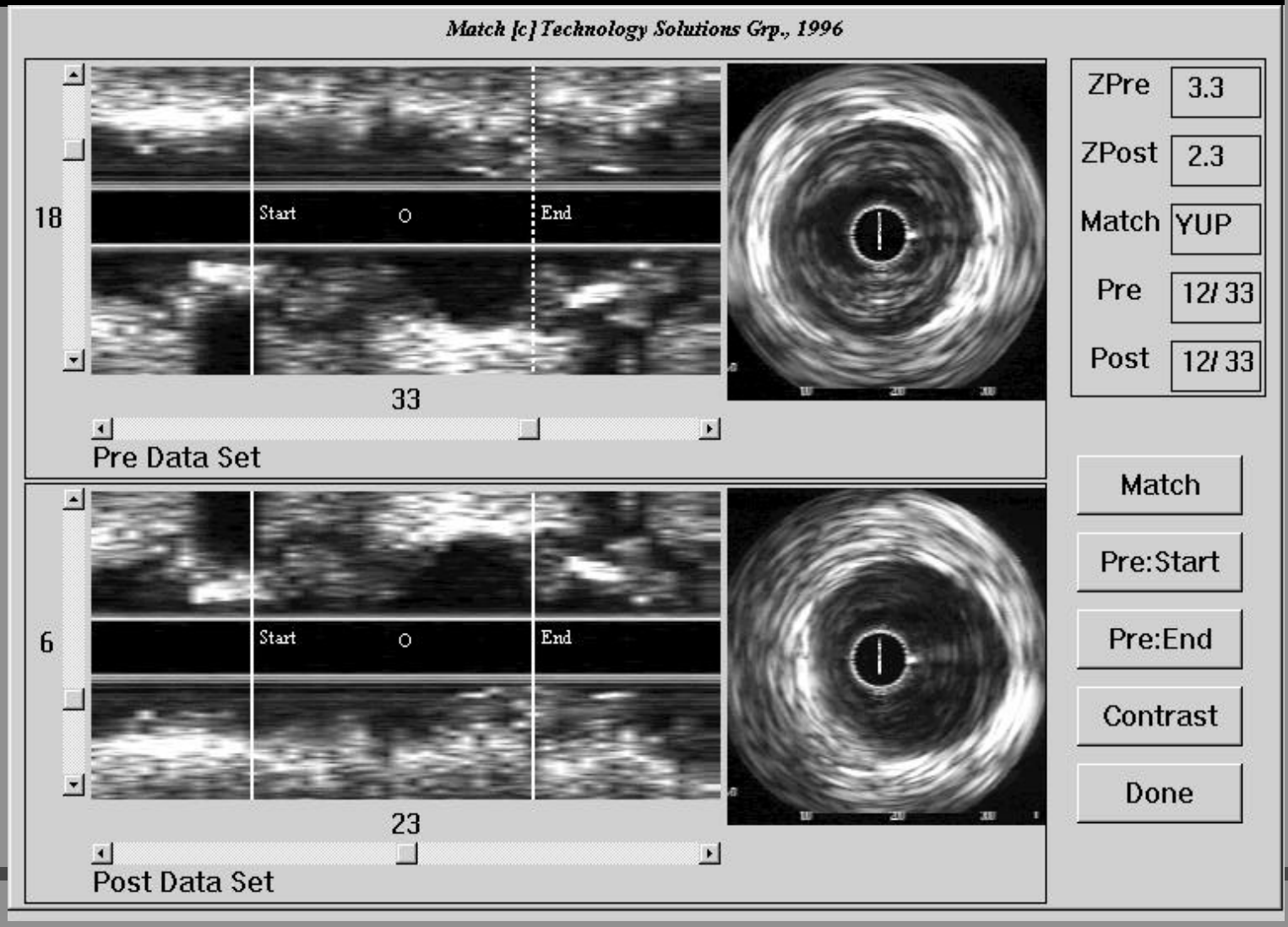
Part 1: The Problem

“3D” IVUS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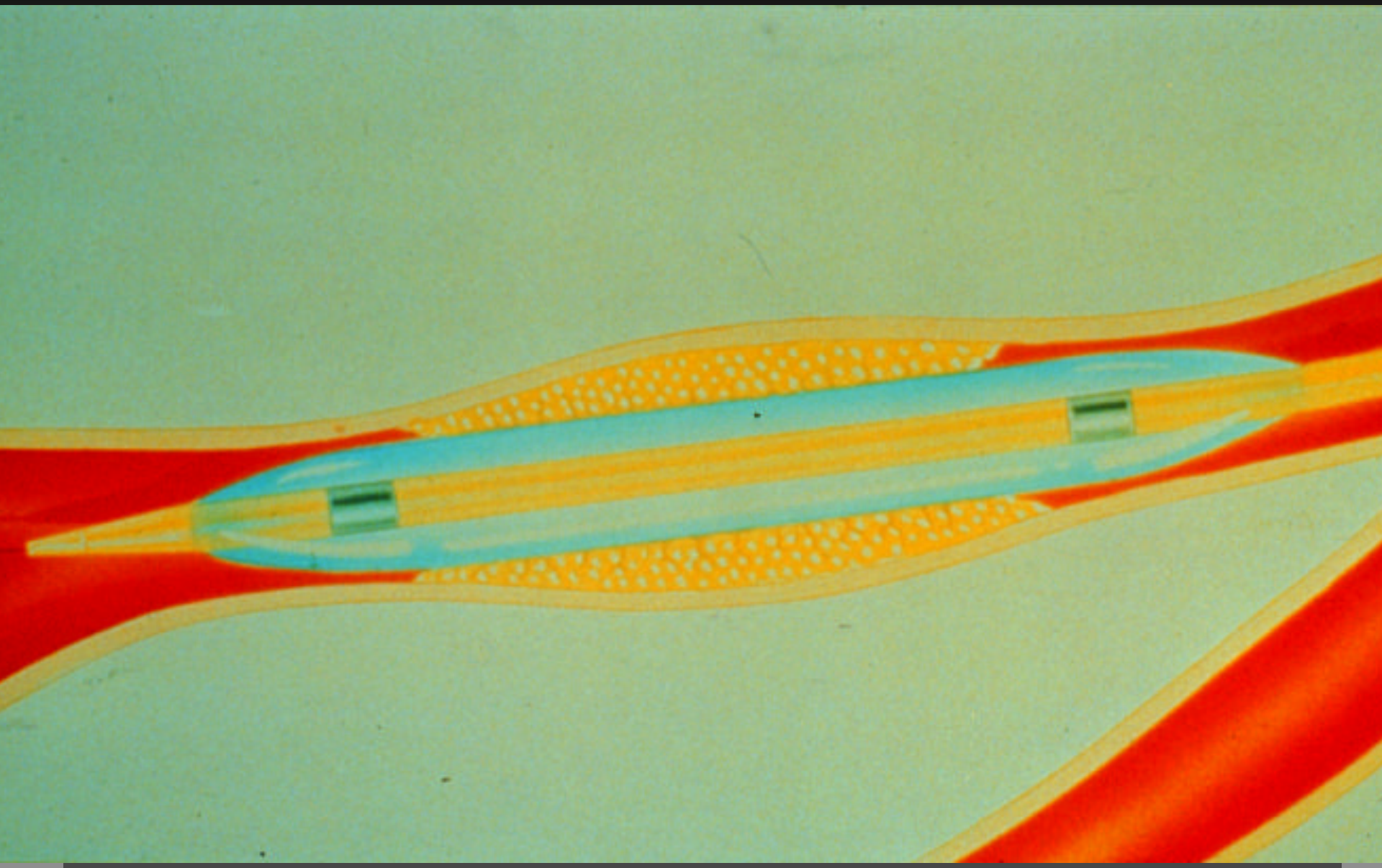
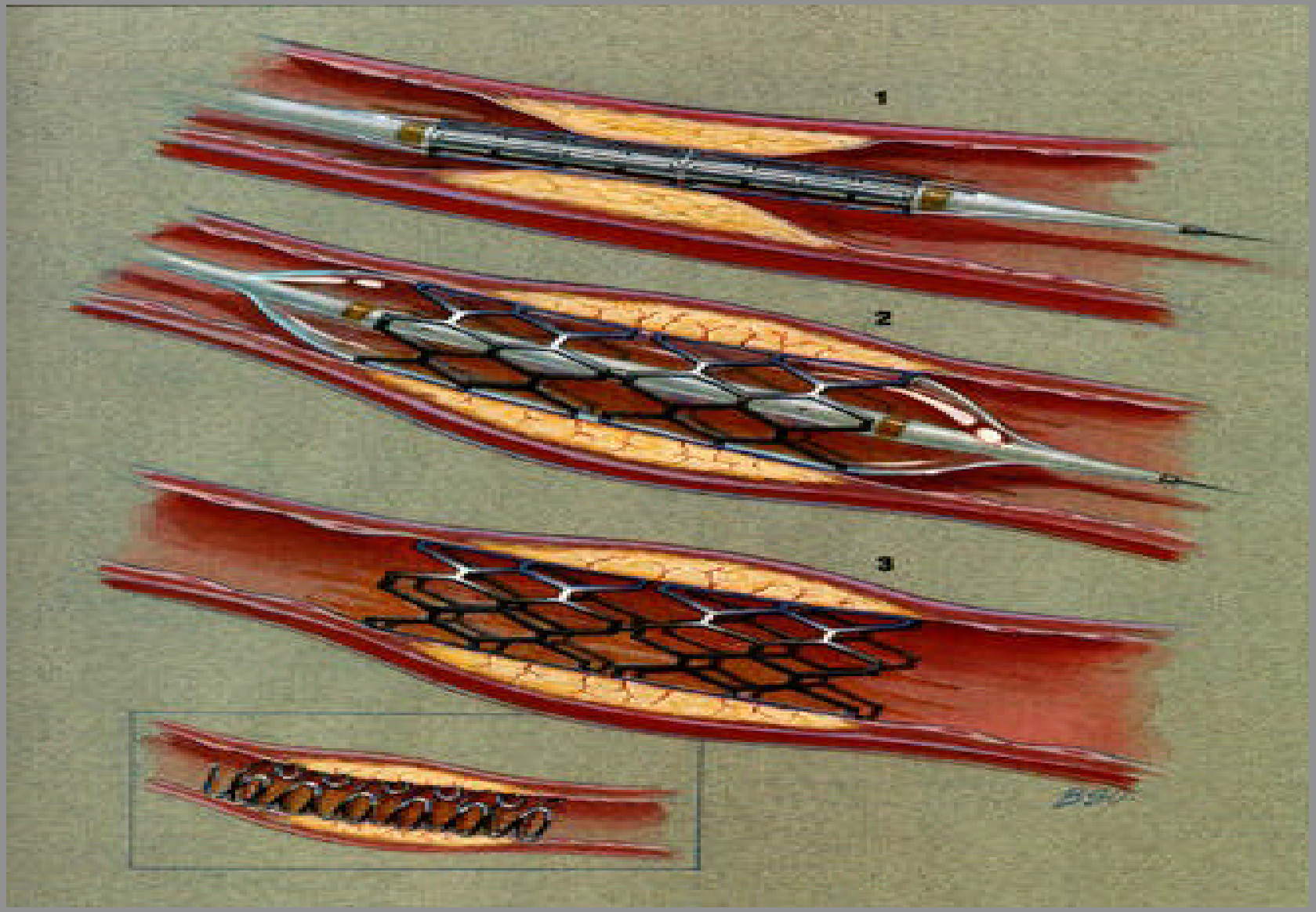


Restenosis vs. Stenosis

- Stenosis takes years to develop.
  - Deposits adhere to artery wall.
  - Smooth muscle covers deposits. Process continues.
- Restenosis (reblockage of the artery) is a response to the angioplasty
  - Angioplasty tears the artery wall.
  - “Scar tissue” forms as part of healing, but fills the lumen.
  - Restenosis happens over a period of months.


1
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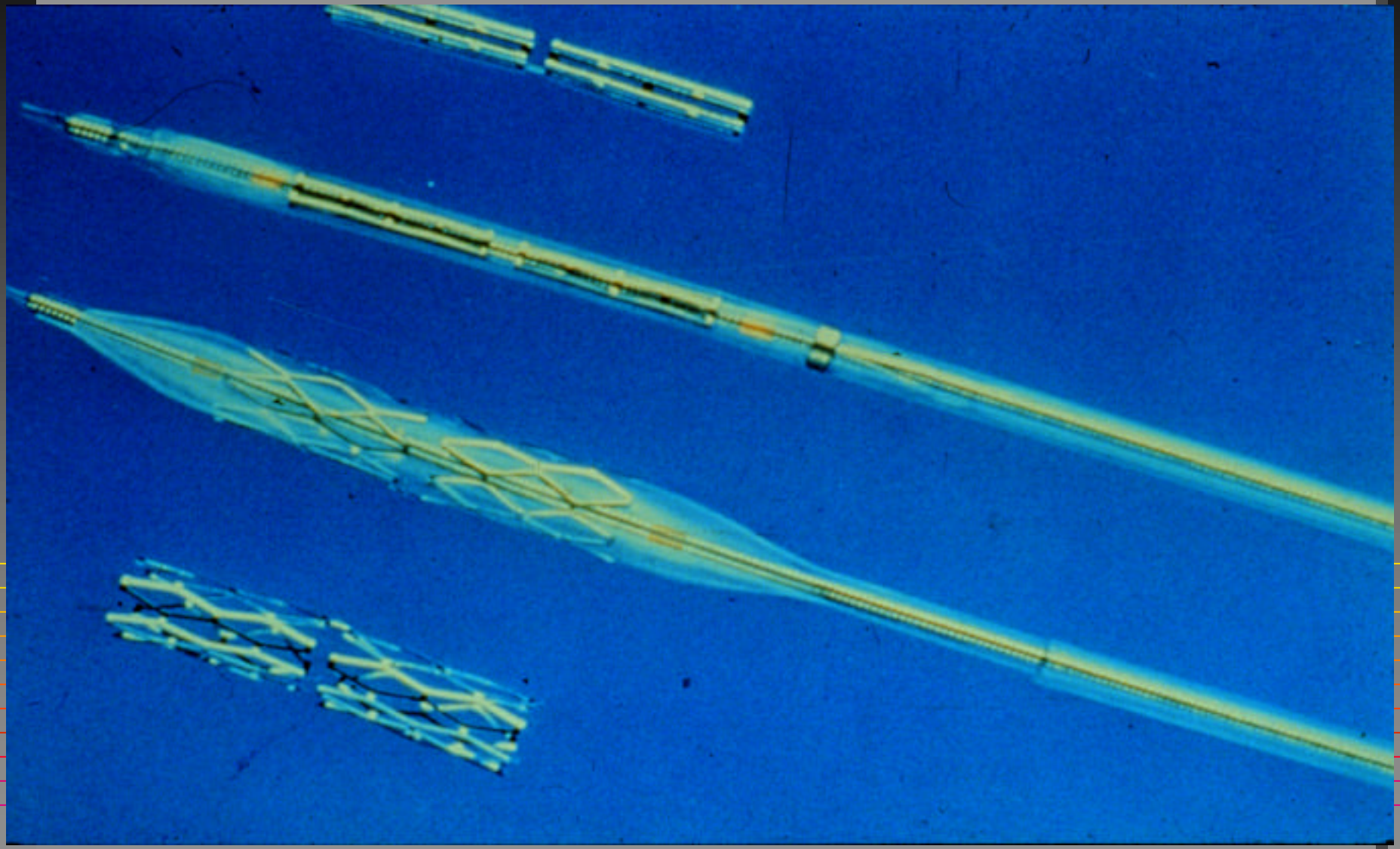
Coronary Stents: Expanded and Compact



Neointimal Infiltrate Through a Stent

Radiation for Restenosis: Background

- Angioplasty of coronary arteries often is followed in a few months by restenosis.
  - About 60% of the time with only angioplasty
  - About 40% of the time with arterial stents
- Radiation appears to reduce the incidence of restenosis to about 10 – 15%.
- But with what dose? To Where? In what time? With what type of source?

Radiation for Restenosis:

Two approaches to the radiation delivery:

- Transcatheter – Use a catheter at the time of angioplasty to hold a very hot source to deliver the dose in 3 to 30 minutes.
- Radioactive stents – Activate the stent that will be placed and irradiate over the life of the source.

Radiation for Restenosis: The underlying problems

- Research and development so far have been based on commercially available sources

  (i.e., commercially driven!)
- Funding agencies are mismatched:
  - Heart, Lung and Blood Institute doesn't support technology
  - National Institute of Standards and Technology doesn't fund outside research
  - National Cancer Institute isn't interested in heart probelms

Part 2: Delivery of Radiation Using Radioactive Stents

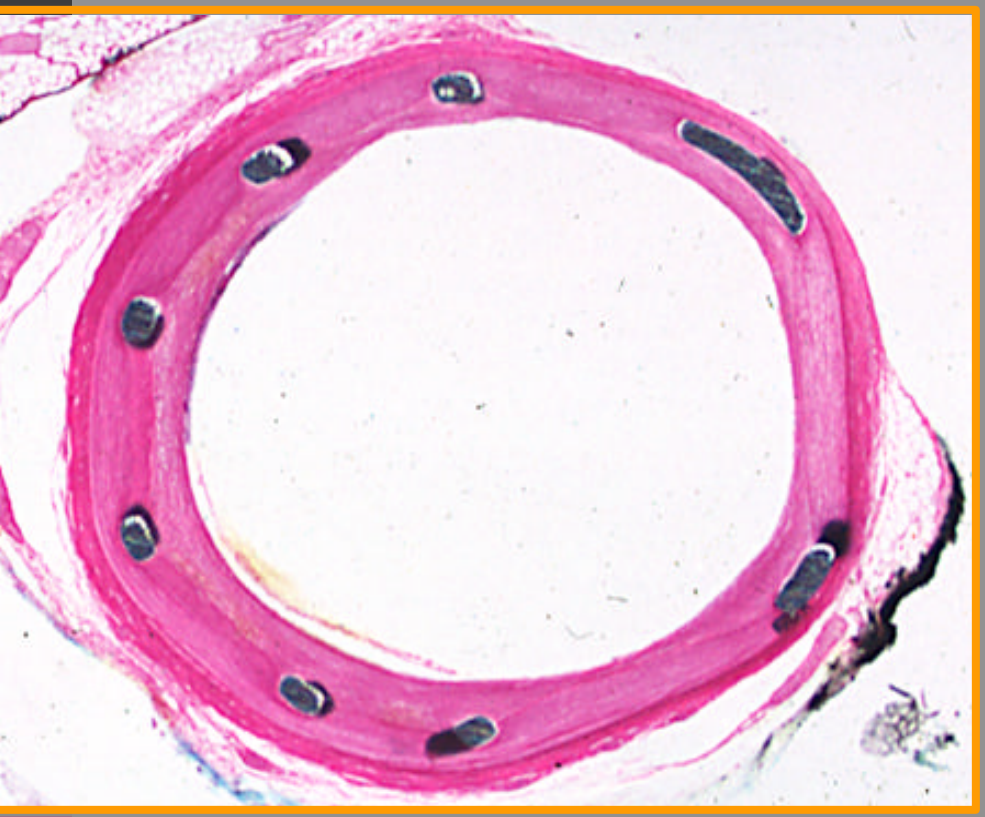
Advantages of Radioisotope Stent Over Catheter-Based Brachytherapy

- Most interventionalists prefer ease, time efficiency and predictability of primary stenting.
- The radioisotope stent essentially eliminates the procedure of catheter-based brachytherapy. More practical for de-novo and multivessel disease
- Safer handling 0.005 mCi of beta vs., up to 500 mCi of gamma source (e.g., Ir 192)

Results of Experiments

Stents worked well in pigs

Radioactive Stents: Porcine Coronary Arteries 1 Month



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Radioisotope Stents : Milan Study Summary

- 10/97-12/98 - 173 P-S and BX ^{32}P stents implanted using SDS delivery system, activity - 0.75-20 μCi.
- No in hospital events; At 1-14 months -> no deaths.
- In stent neointimal area reduced in a dose-dependent fashion.
- Overall restenosis ranged from 39-55% with nearly all restenosis due to edge restenosis.

rom Colombo, et al, as presented CV Radiation Therapy III, 2/99.

Radioactive Stent Analyses

Albiero et al. Circulation. 101: 18-26 (2000)

- Calls attention to Moses, J Am Coll Card 31: 350A (1998), 0.75 - 1.5 mCi ^{32}P stents yielded 40% restenosis, a little higher than control.
- Albierto fount 3 mCi worked better.
  - Maybe the low-activity stents induce more injury response
  - None radioactive stents do
- Saw little intrastent neointima but did see on edges (more distally than proximally).

Radio-active Stent Analyses

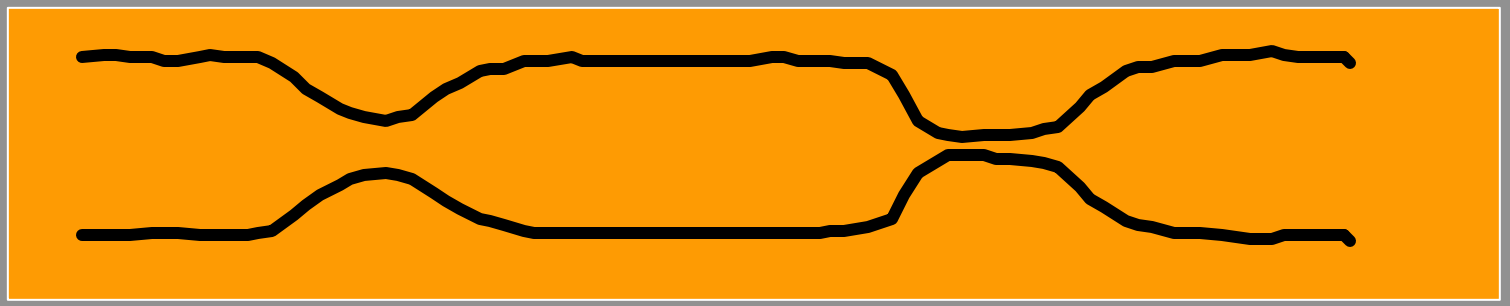
TABLE 5. Follow-up Intralesion Quantitative Angiographic Measurements

	Group 1, 0.75–3.0 μCi	Group 2, 3.0–6.0 μCi	Group 3, 6.0–12.0 μCi	P
No. of lesions, n (%)	19 (70)	29 (91)	26 (81)	
Follow-up				
Reference diameter, mm	3.17±0.42	3.13±0.39	3.17±0.41	NS
MLD, mm	1.60±1.08	1.90±0.90	1.74±1.15	NS
%DS	51±33	39±29	46±35	NS
Lesion length, mm	12.7±8.4	13.8±6.1	17.6±7.5*	0.048
Acute gain	1.9±0.38	2.3±0.44	2.3±0.50	NS
Late loss	1.53±0.90	1.26±0.82	1.20±1.05	NS
Loss index	0.71±0.42	0.59±0.43	0.57±0.52	NS
Intralesion restenosis, %DS≥50	10 (52)	12 (41)	13 (50)	NS
Type of restenosis, n (%)				NS
No restenosis	9 (48)	17 (59)	13 (50)	
Pure intrastent	3 (16)	1 (3)	0	
Total occlusion	1 (5)	0	3 (11)	
At the edges	5 (26)	8 (28)	9 (35)	
At the edges+intrastent	1 (5)	3 (10)	1 (4)	

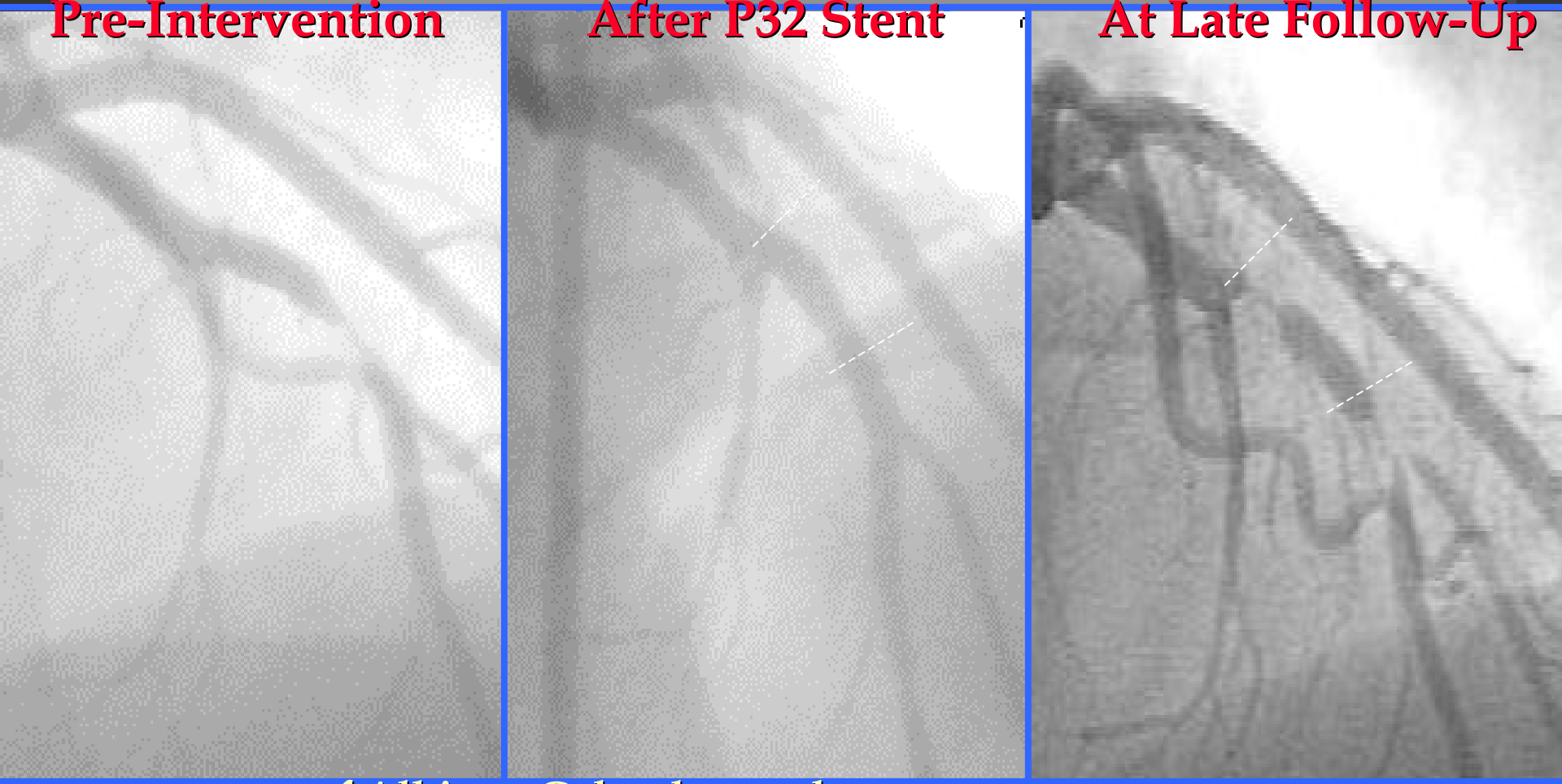
*Significant difference between group 3 and group 1.

Albiero et al. Circulation. 101: 18-26 (2000) - 2

Candy Wrapper Restenosis



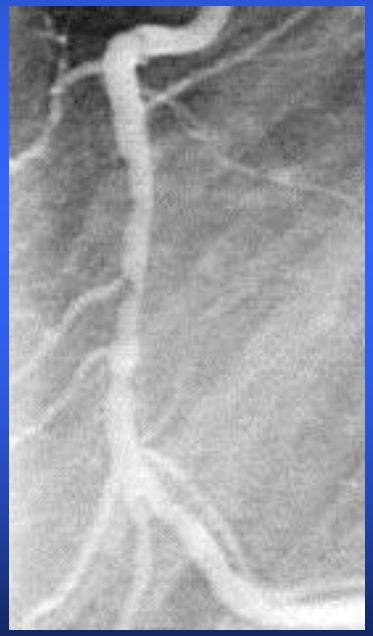
"Candy Wrapper" Restenosis After P32 Stent



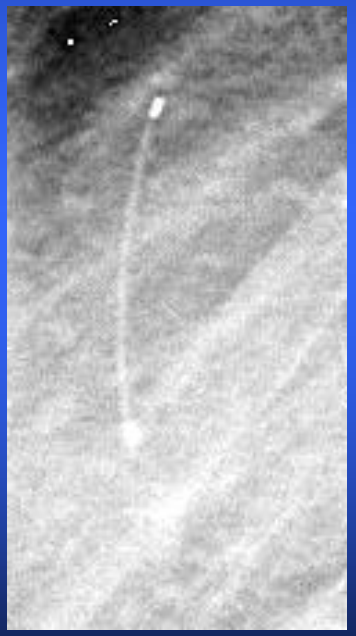
Images courtesy of Albiero, Colombo, et al.

Edge Effect

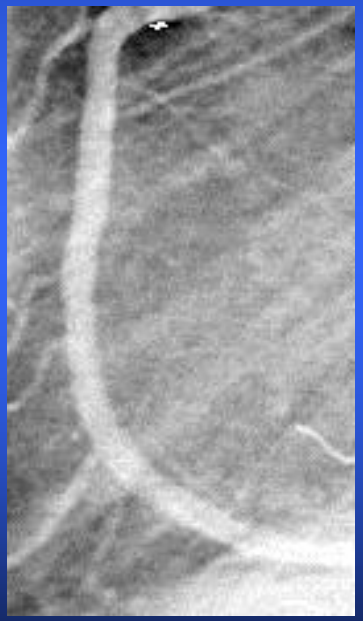
Pre-Dil



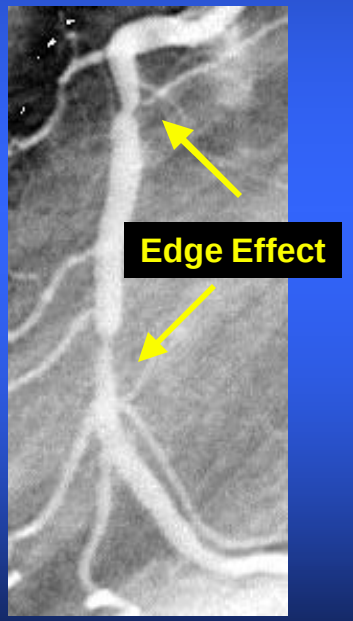
Irradiation
30mm RST



Final
Post 25mm Stent
on 29mm balloon



F-U

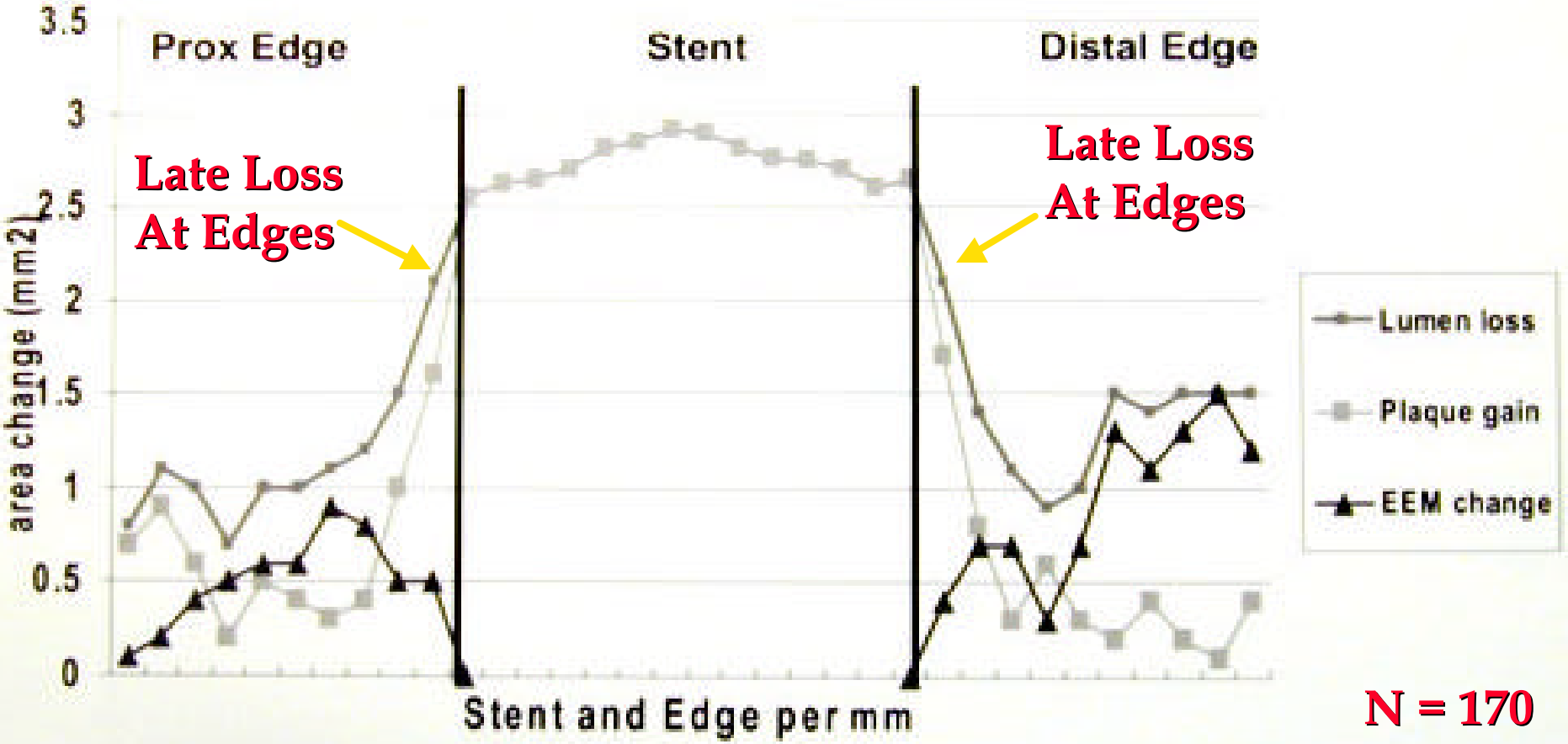


Radioactive Stent Analyses

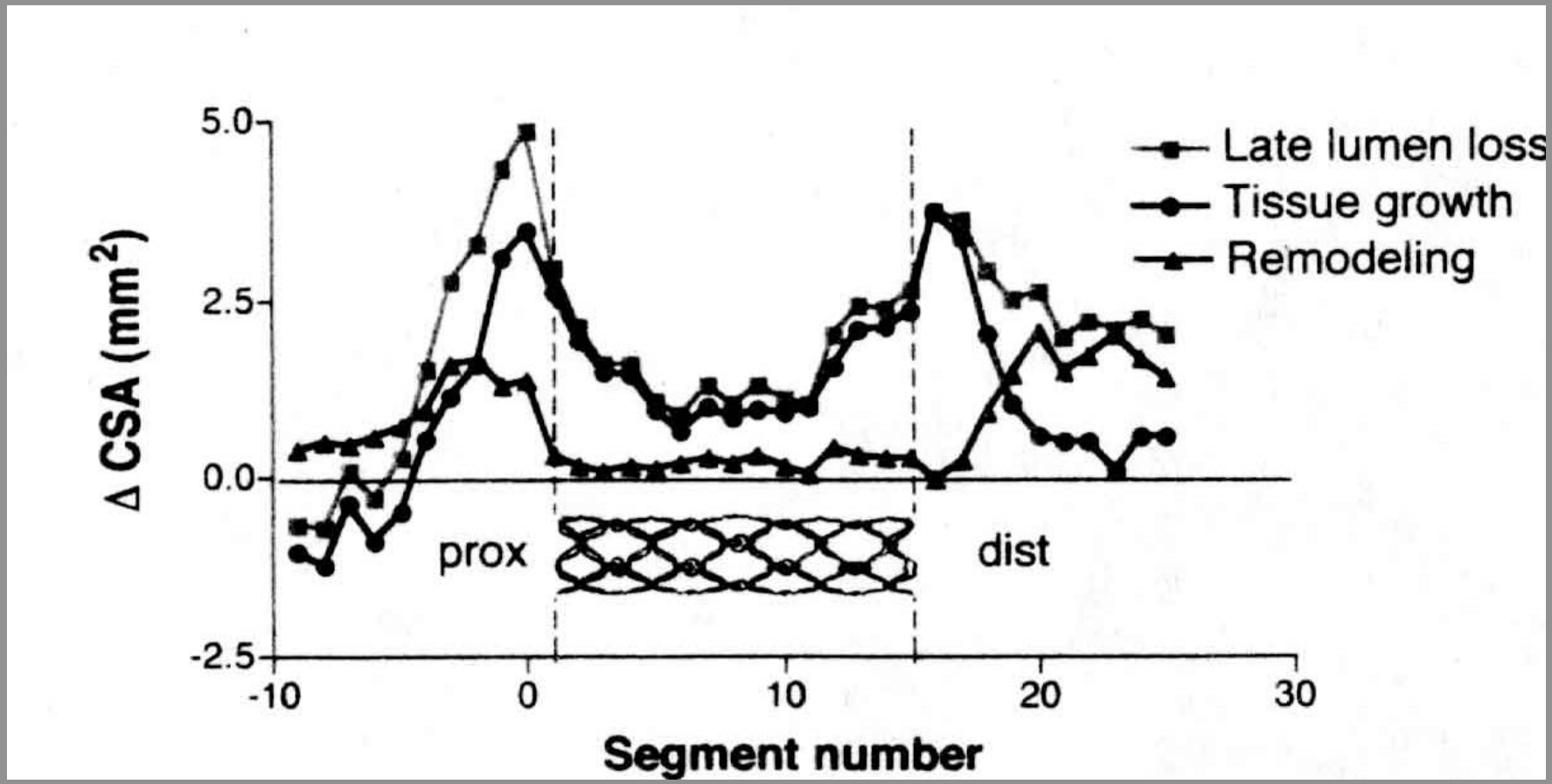
Albiero et al. Circulation. 101: 18-26 (2000) - 2

- End effect could be due to low doses at the ends and high balloon to artery ratio.
- Hypothesizes that low activities, when they work, may inhibit smooth muscle migration into the lumen, but higher activities may deliver adequate doses to the deeper parts of the artery to inhibit proliferation.

Pattern of Neointimal Hyperplasia (by IVUS)
Non-radioactive P-S Stents



Radioactive Stent Analyses



Albiero et al. Circulation. 101: 18-26 (2000) - 2

Radioactive Stent Analyses

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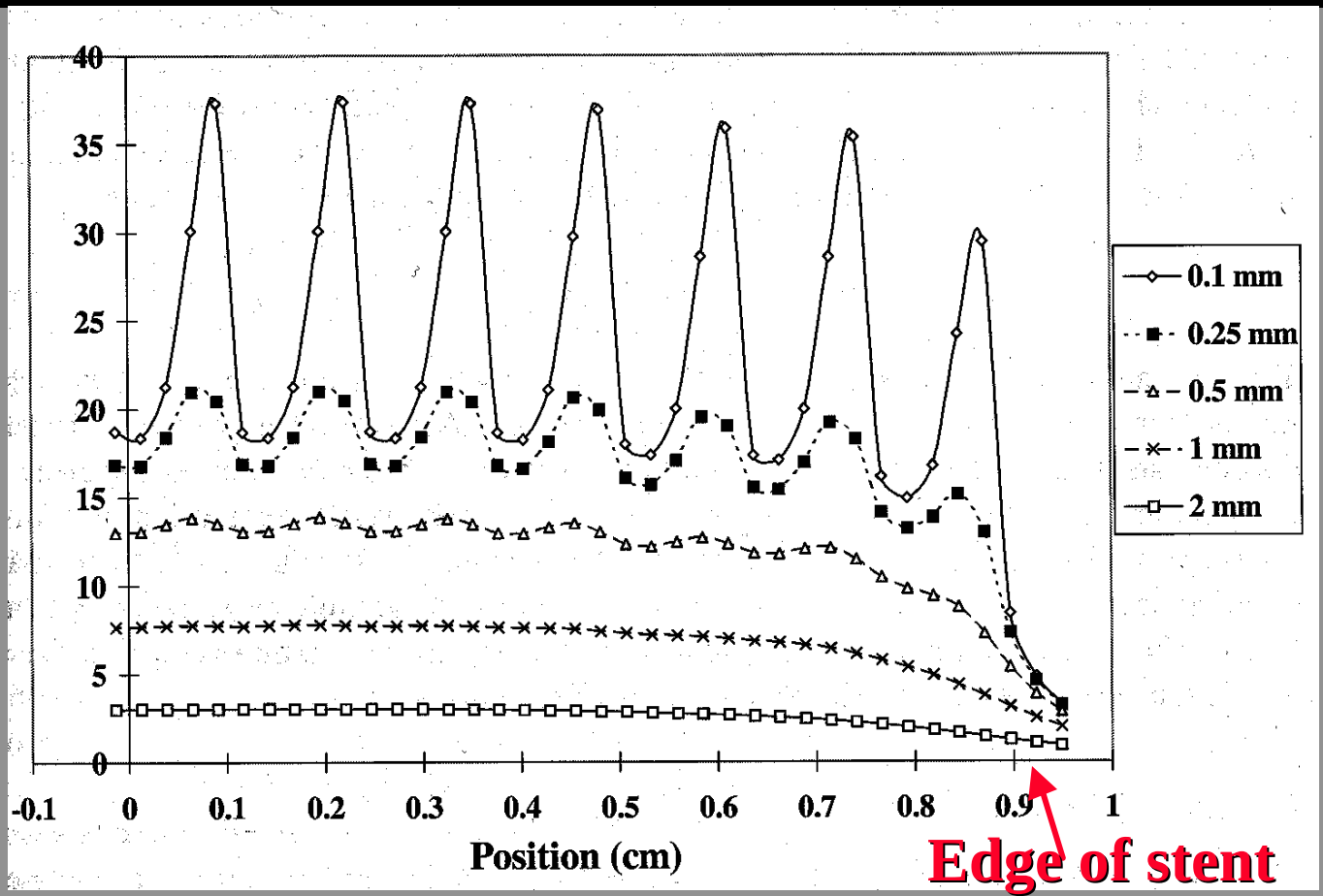
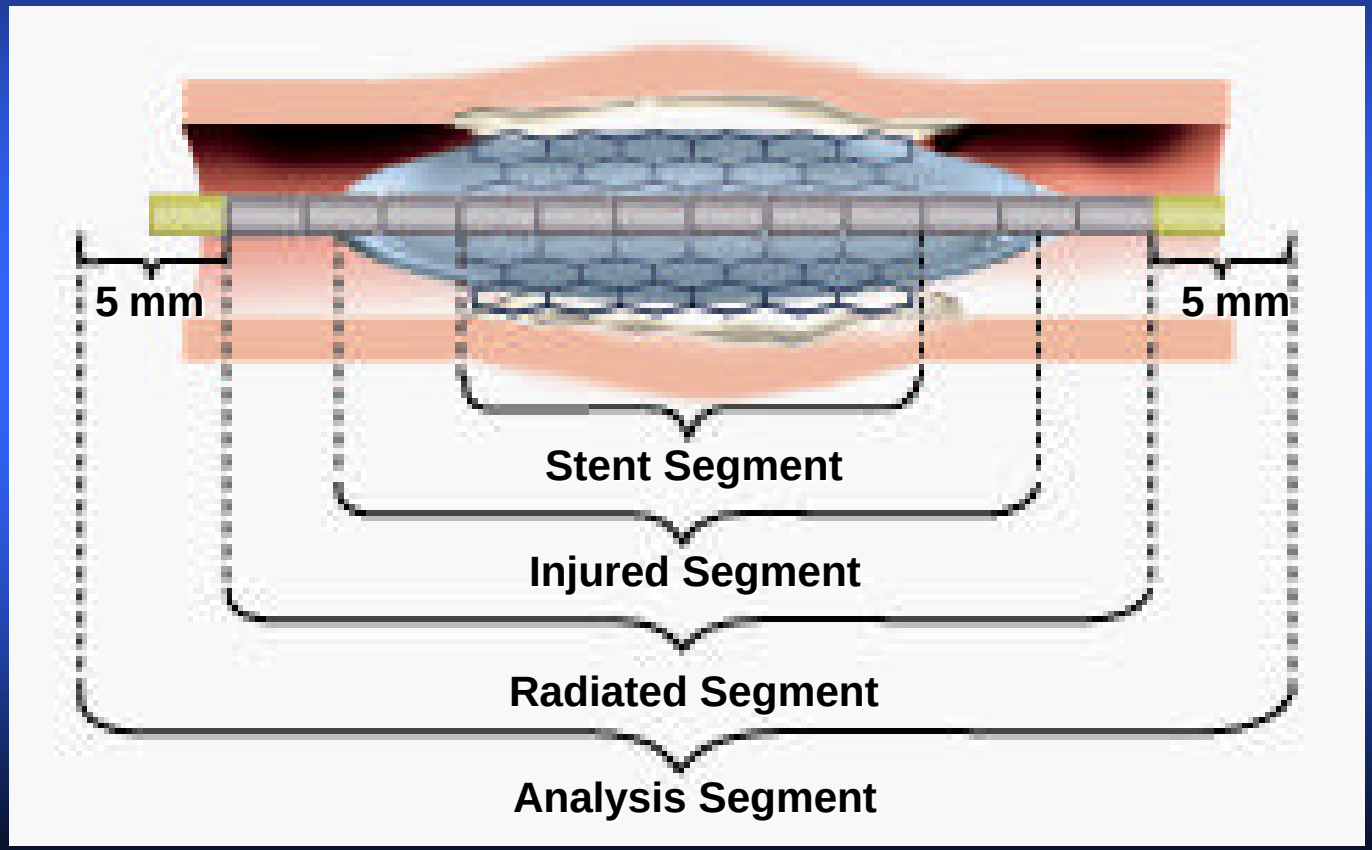
^{32}P Stent Dose Profiles [Gray/MBq for 18.2 mm long stent]



Fox and Henson, Phys. Med. Biol. **45** (2000):3643-36

START

8 Month Angiographic QCA Analysis



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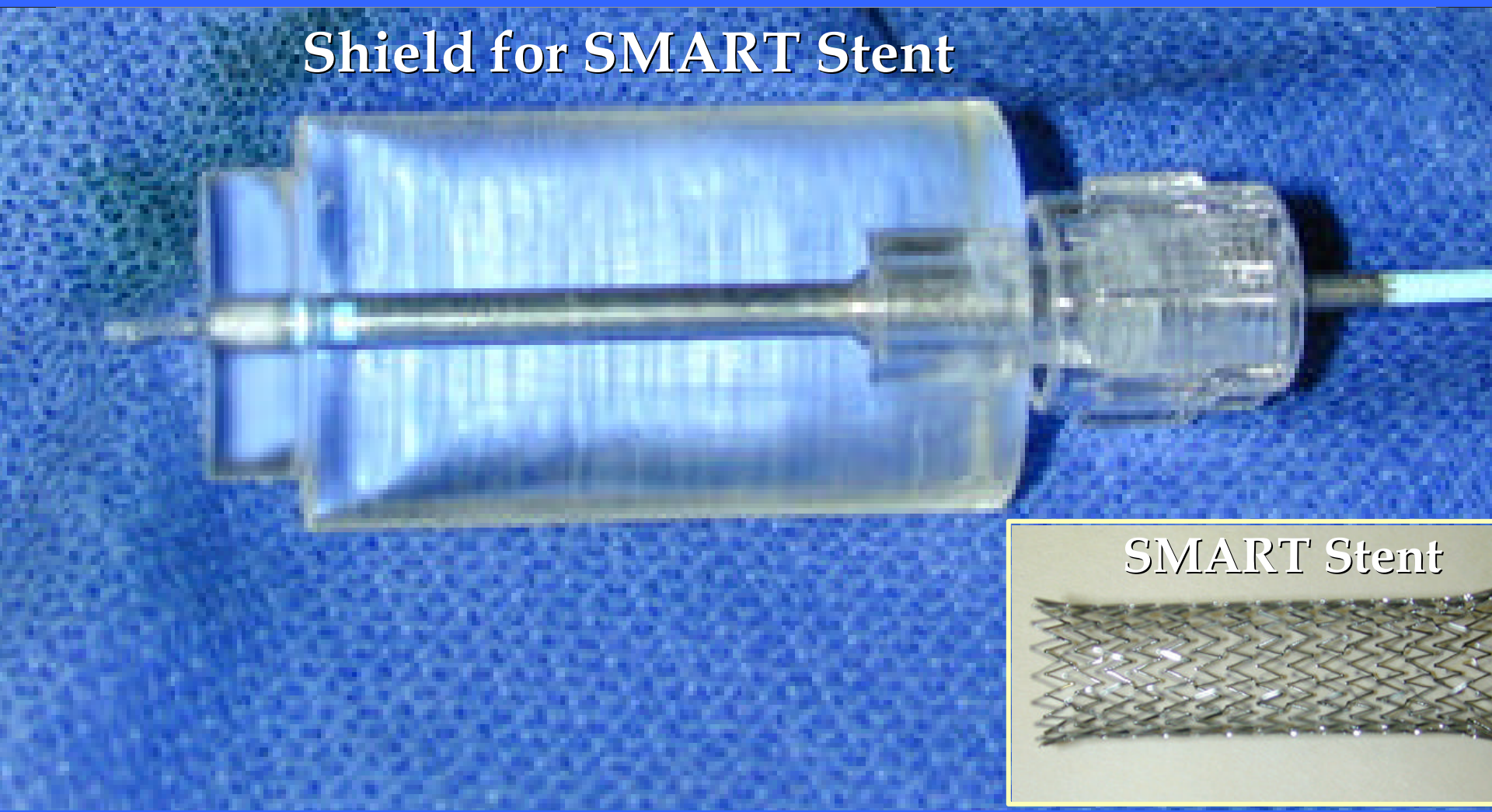
Attempts to Prevent Candy Wrapper Effects

- Adding non-active lengths to the ends of a stent
- Making the ends of the a stent hotter

P32 Self-Expanding SMART Stent

Shield for SMART Stent



SMART Stent

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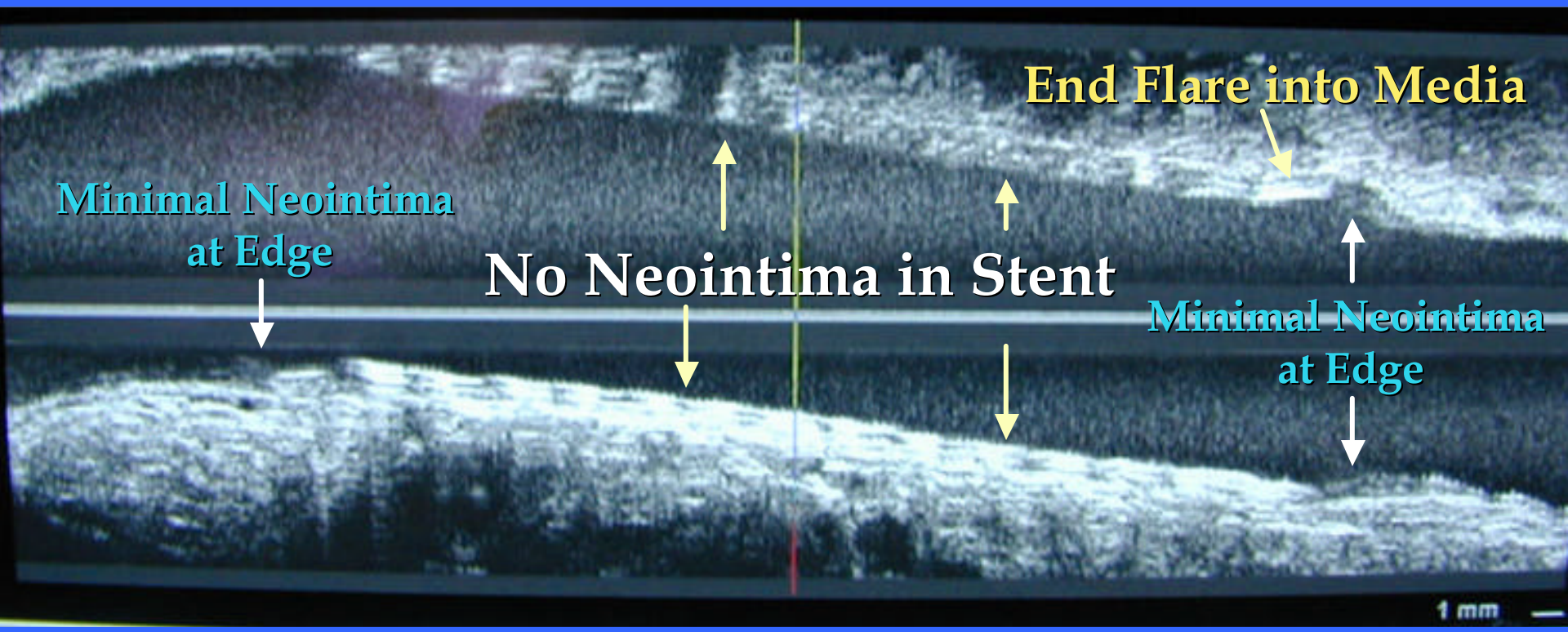
Rationale: Self-Expanding Radioisotope Stent

- Current animal and clinical data suggest that edge restenosis is interplay between injury and low-dose falloff outside stent.
- Difficult to deliver balloon expandable stent with < 1.0 mm injury zone outside stent edge.
- Self-expanding (e.g., nitinol) stents can be delivered to treated segment with no barotrauma beyond the stent edge.

Longitudinal IVUS Porcine Iliac
P32 SMART Stent at 30 Days (Pig 1)



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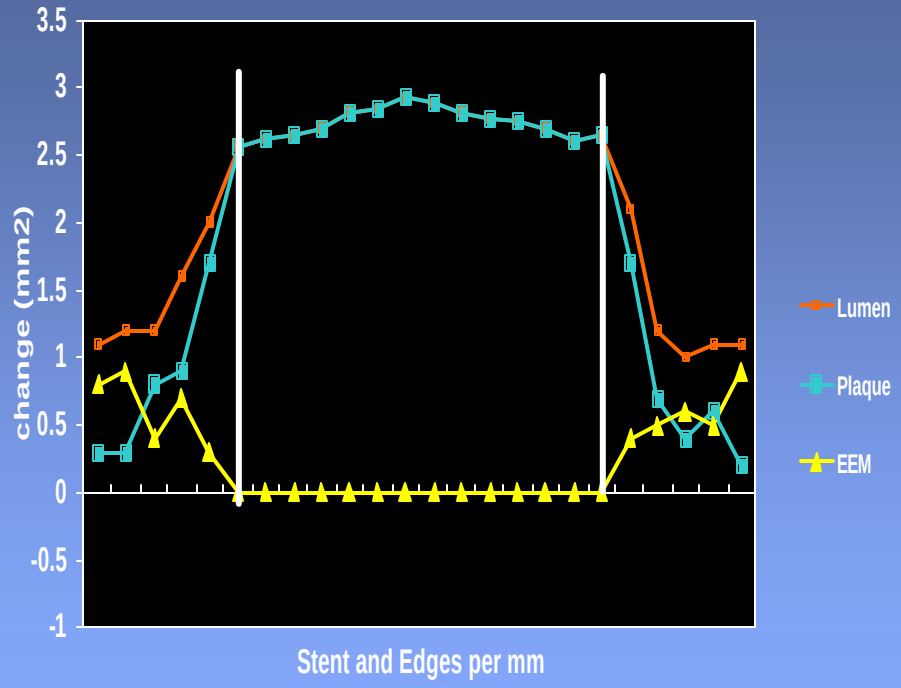
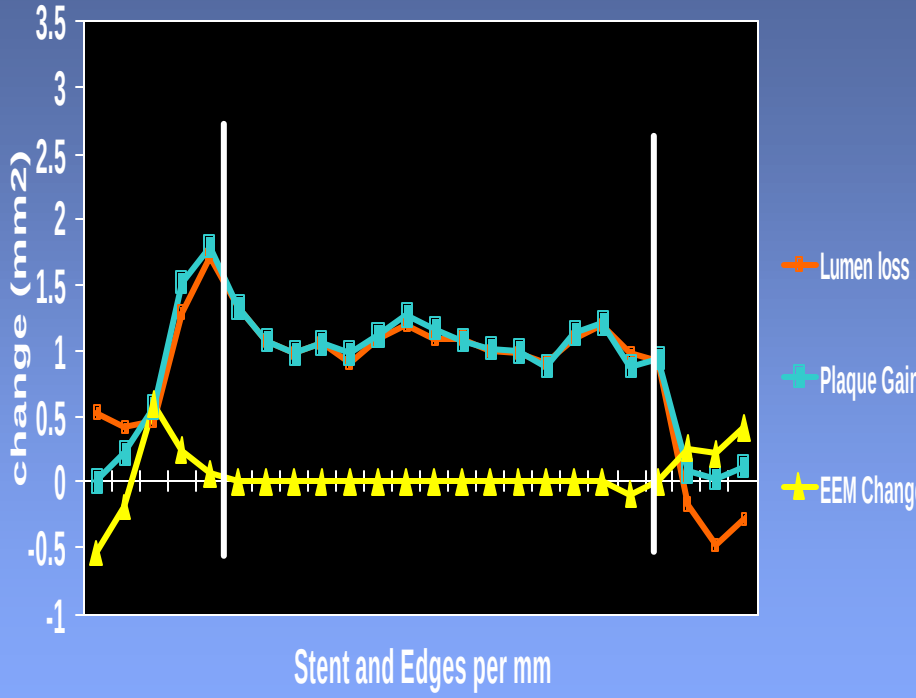
Serial IVUS Analysis Radioactive Stents

"Hot Ends" P32 Stents; N = 59 vs. Nonradioactive

Non-Radioactive



'Hot Ends'



From Neil Weissman, et al., 2000

Attempts to Prevent Candy Wrapper Effects

- Adding non-active lengths to the ends of a stent
- Making the ends of the a stent hotter

Neither had any effect

Attempts to Prevent Candy Wrapper Effects

- Adding non-active lengths to the ends of a stent
- Making the ends of the a stent hotter

Neither had any effect

- Try different radionuclides

Characteristics of ^{32}P

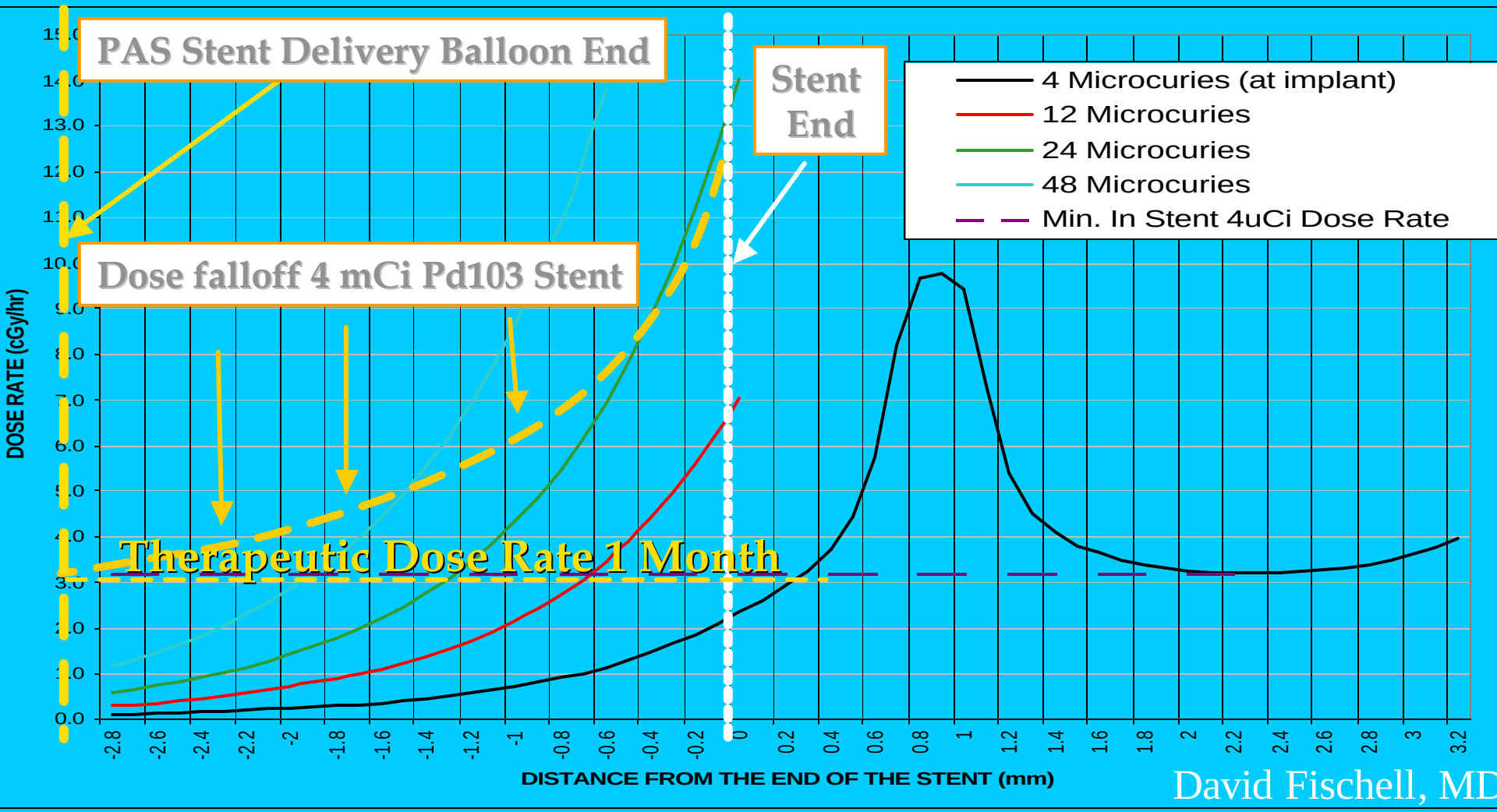
- Pure beta emitter - protection is easy and no external hazard.
- Range covers the adventitia.
- Half life 14 days - seemed to match the time course for restenosis.

BUT…

Rationale for Development of Gamma Stent

- Beta particle emitting stents have limited range of dosing to tissue outside stent edge (~1.5 mm).
- Gamma stent (e.g. Pd 103) could increase therapeutic dosing range to 2-3 mm outside stent edge.

Dose-rate Beyond Ends of P32 Vs Pd 103 Radioisotope Stent at 1 Month



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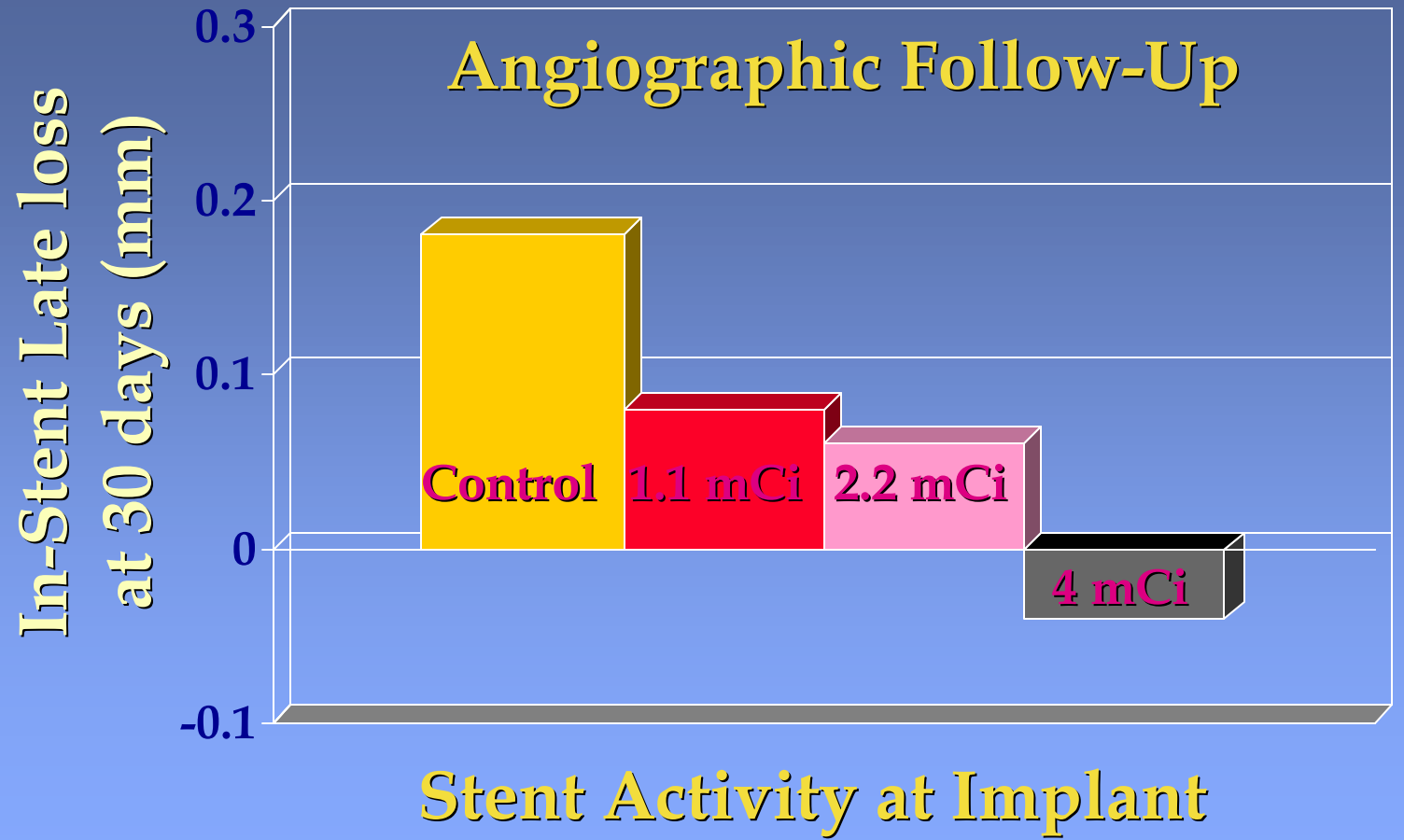
Palladium 103 Rabbit Iliac Late Loss 30 Days



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Low Doses at the Ends

- There is very good evidence that doses just below the treatment levels can make restenosis worse.
- Thus, if the ends are injured but insufficiently treated, that more increase the incidence of restenosis.

Timing of Treatment Delivery

- The 14 day half life of ^{32}P or 17 day of ^{103}Pd seemed to match the biology of restenosis in the earlier understanding.
- Now we know that the radiation is most effective about 1 - 2 days after the angioplasty, and does no good after a week.
  - So most of the radiation from these radionuclides comes too late.
  - Would like a short lived radionuclide.
- Except, maybe would like a very long lived stent to stave off restenosis for long time.

Summary of Radioactive Stents

- We don’t know what the best radionuclide engine is.
- Experiments are needed to determine the optimum.
- Several steps are needed to prepare for such experiments.

Part 3: The University of Wisconsin Radioactive Stent Project

Goals of Our Research

- **Major Goal: To provide the physical and technical infrastructure for solid biological experiments to find the optimum radionuclide for radioactive stents.**
- **Subsidiary Goals:**
  1. **Find ways to manufacture stents with various radionuclide engines.**
  2. **Develop methods to establish meaningful source strength for the sources.**
  3. **Develop techniques for accurate *in-vivo* dosimetry for stents in patients.**

Part 1: Source Development

Making the radioactive stents requires two steps:

1. Generating the isotopes using the UW TRIGA reactor or the Medical Physics Cyclotron, and
2. Associating the source with the stent, which requires
   - Fixing the radionuclides to the arterial stent.
   - Controlling the quantity of the radionuclide.
   - Differentially activating the stent.

The order of the steps varies with the radionuclide.

Some Methods of Activating Stents

- Straight Activation – Make the stent out of a target material and activate in a radiation beam: examples, ^{48}V or a slew from stainless steel.
- Radionuclide to stent – Make the radionuclide and “coat” the stent: Example, the former commercial ^{32}P Stents.
- “Coat” stent then activate – Place the target on the stent and then activate: Example, ^{197}Au coating activated to ^{198}Au.

Our Work So Far

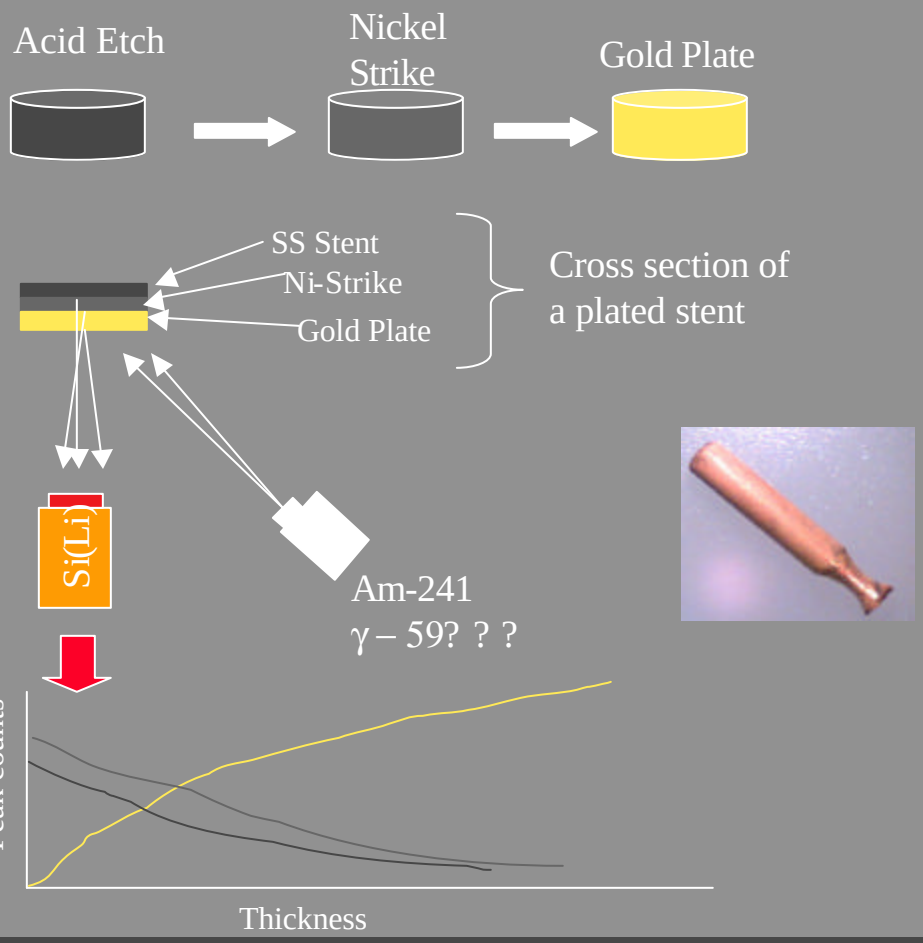
We started with the manufacture of ^{198}Au

- Half life of 2.7 days may deliver the radiation in a time that matches well the biology.
- The photon radiation should carry the dose farther beyond the end of the stent.

We electroplate the stable gold into the stainless steel stent, and activate in the TRIGA reactor.

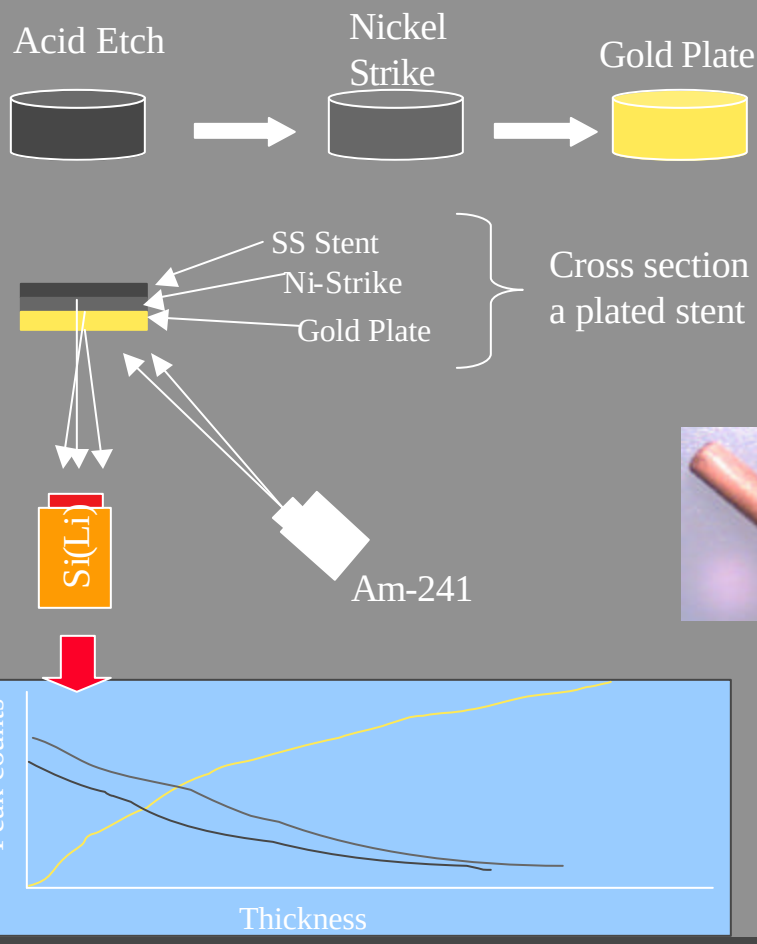
- The electroplating allows fine control of the thickness of the material and, thus, the source distribution => Dose distribution.
- The electroplating has proven stable and leaches little.

The Art of Stent Plating



- Raw stent is etched in acid.
  - Cleans the surface.
  - Prepares for the nickel strike.
- Stent is weighed before and after coating as measure of surface coating.
- Good success in making uniform coatings.

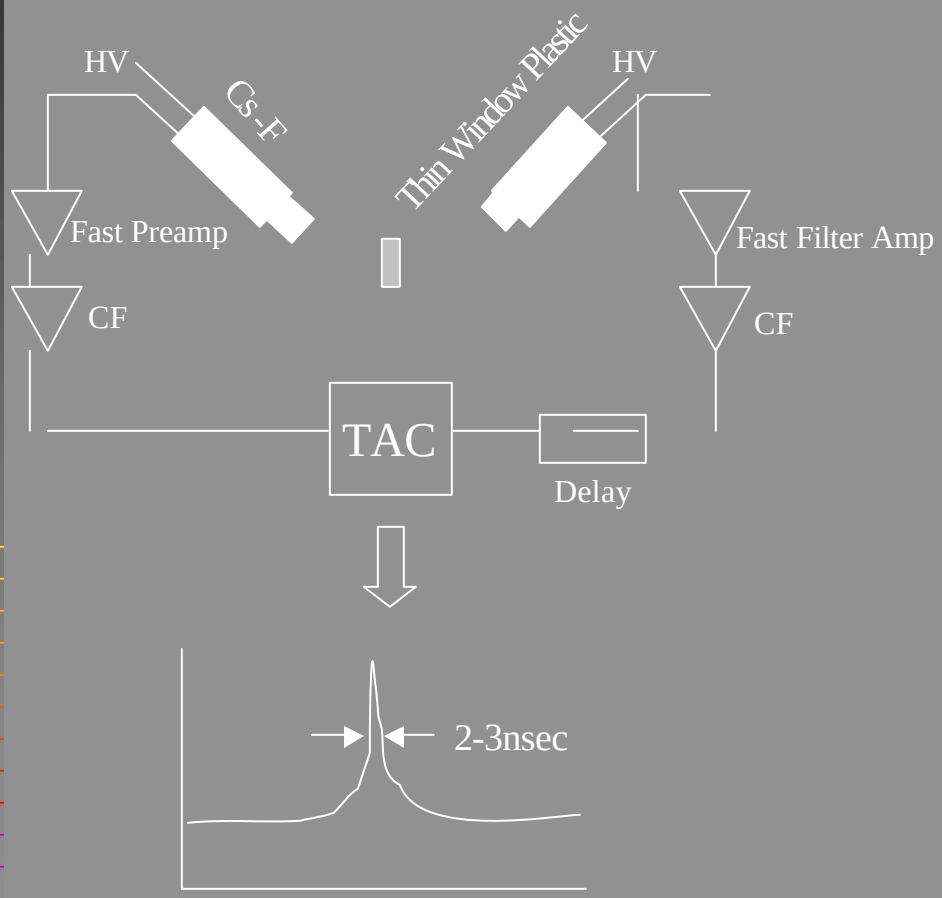
The Art of Stent Plating



More accurate assessment of the gold coating using x-ray fluoroscopy,

- Detecting excited L-shell transitions using the 59keV gamma-ray of Am-241 and a Si(Li) detector.
- As the plating thickness increases the counts under the peaks for L-shell transitions in gold will increase and those from the nickel strike and stainless steel base will decrease.
- Compare with light microscopy.

Assay of ^{198}Au-Stent Activity



Assay of activated ^{197}Au plated stents through the (n,γ) ^{198}Au reaction will be done with a thin window plastic (beta) and Cs-F (gamma) scintillating coincidence pair. The two decay lines of interest are the β^- 1.371 MeV, and g 411keV. Several trials have been done with β^-, g isotopes achieving coincidence peak resolutions on the order of a few nanoseconds. A ^{198}Au source is still needed to calibrate the detector setup, however, the results achieved with the dummy sources are promising.

Part 2: Calibration Studies

- Determining the activity of the sources is necessary for us to assess production, but…
- Activity is not a good strength indicator for dosimetry because small variations in the platform can vary output greatly.
- Calibration standards are necessary for a basis of the patient dosimetry.
- NIST doesn’t have standards for any of these sources since they are, as yet, unique.
- So, we need to develop calibration standards.

Problems with Calibrating Radioactive Stents Source Strength

- Beta and/or gamma sources
- Quantity for “source strength”
  - Normal brachytherapy uses air kerma strength.
  - Some IVB beats use dose rate at 2 mm.
- Low activities
- Uncertain geometries
  - For standardization will use undeployed stent
  - Leave the effect of deployment for the third part of the project.

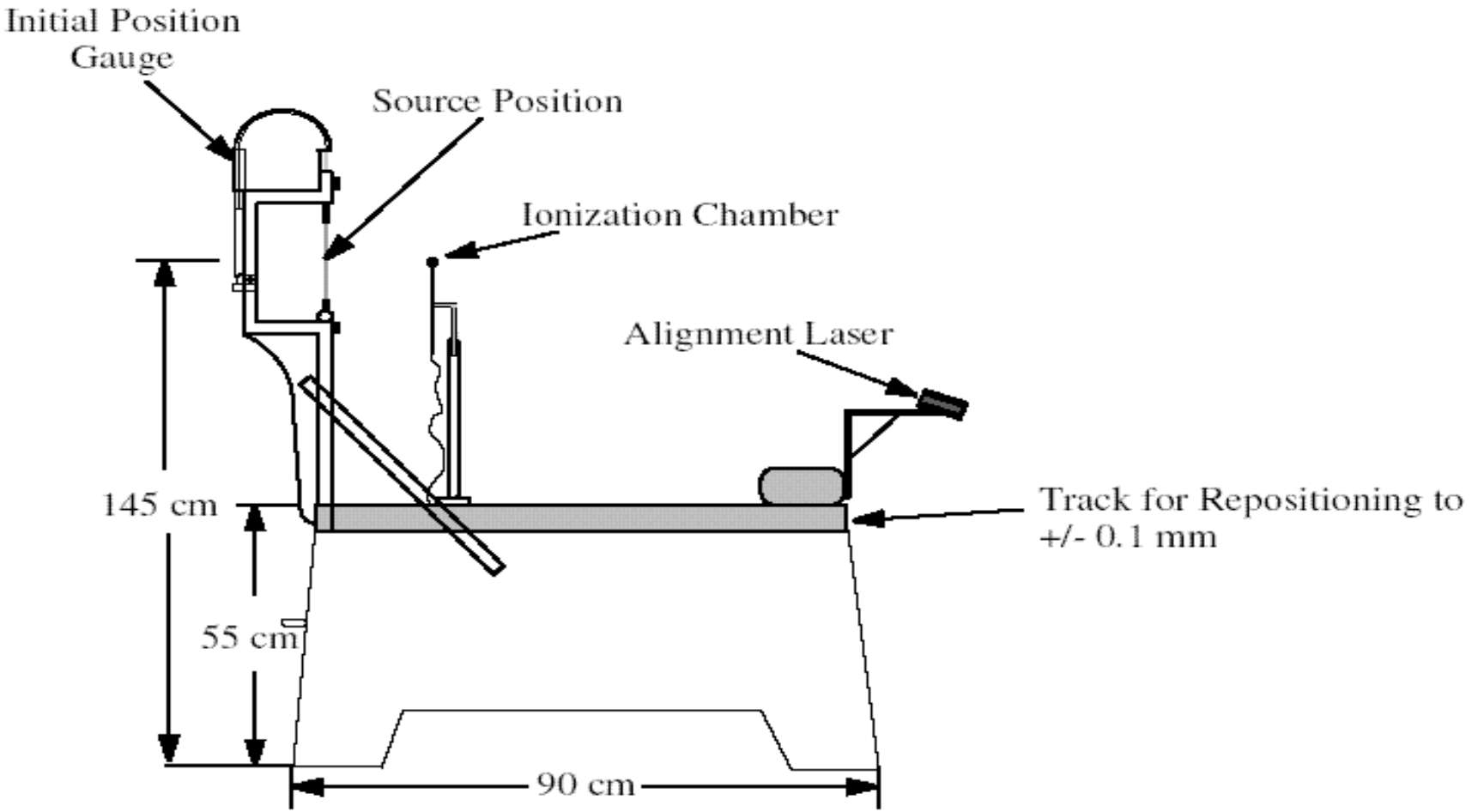
Coronary Stents: Expanded and Compact

Calibration for Gold Stents

This first one is easy.

- **Can make them very active.**
- **Can filter the betas and calibrate similarly to ^{192}Ir using the seven-distance techniques.**

Seven Distance Measurement Apparatus



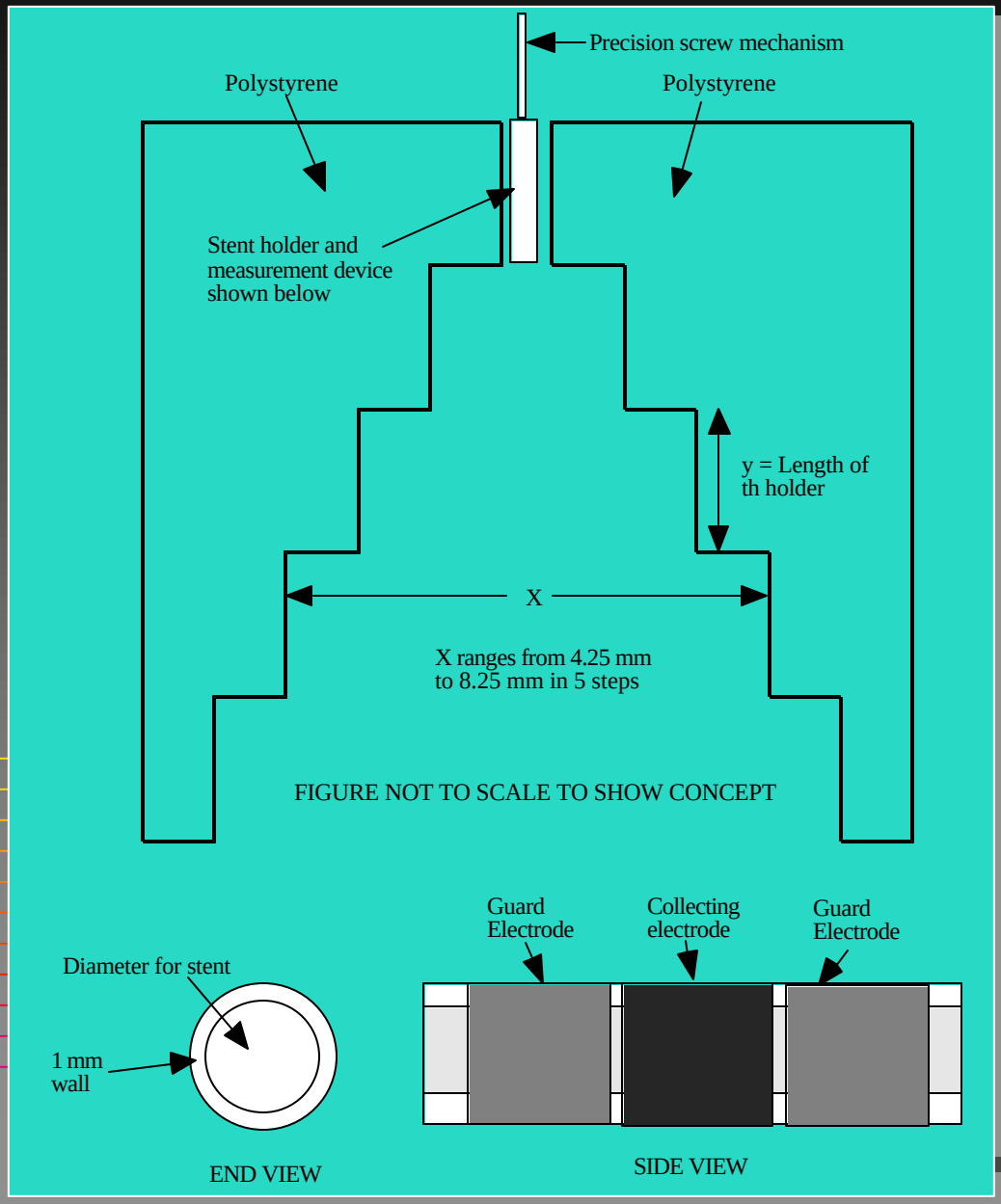
For Other Sources

- Low energy gammas, or
- Beta sources, or
- Low activity sources,

We will not be able to perform the distant measurement.

For these we are developing a new extrapolation chamber.

UW Brachytherapy Extrapolation Chamber



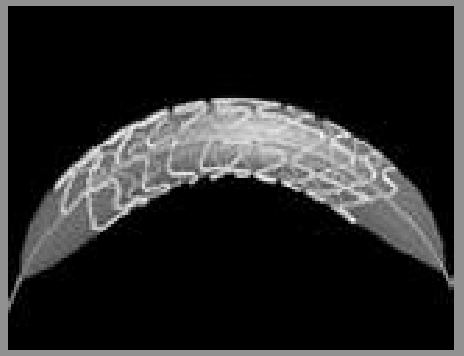
Part 3: *In-vivo* Dosimetry

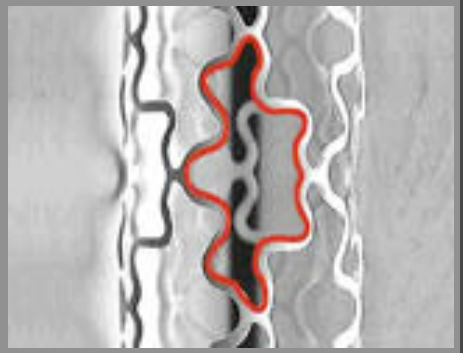
The deployed stent will produce a very different dose distribution than the undeployed stent.

Dosimetry Problems

Problems with finding dose distributions

- Very short distances
- Beta sources
- Uncertain positions in the arteries
- For stents, describing the source geometry
- Curvatures



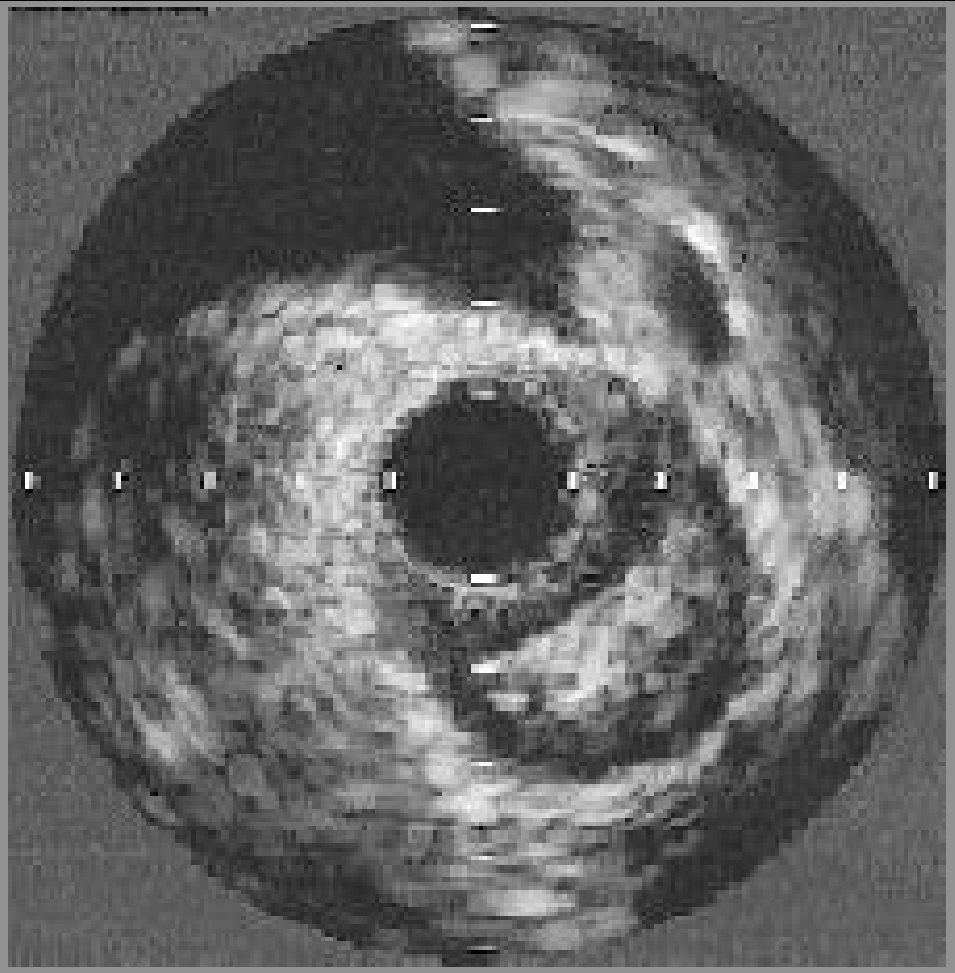


Our dosimetry Approach

Our approach takes several steps:

1. Determine the dose distribution around a small piece (or small pieces of different size and shape - struxels) per unit source strength using Monte Carlo.
2. Find the geometry of the stent by intravascular ultrasound (IVUS).
3. Calculate the dose distribution for each struxel in each “transverse” cut of the IVUS.
4. Create a summation dose distribution.

Dosimetry Based on IVUS



Forming the Summation Dose Distribution

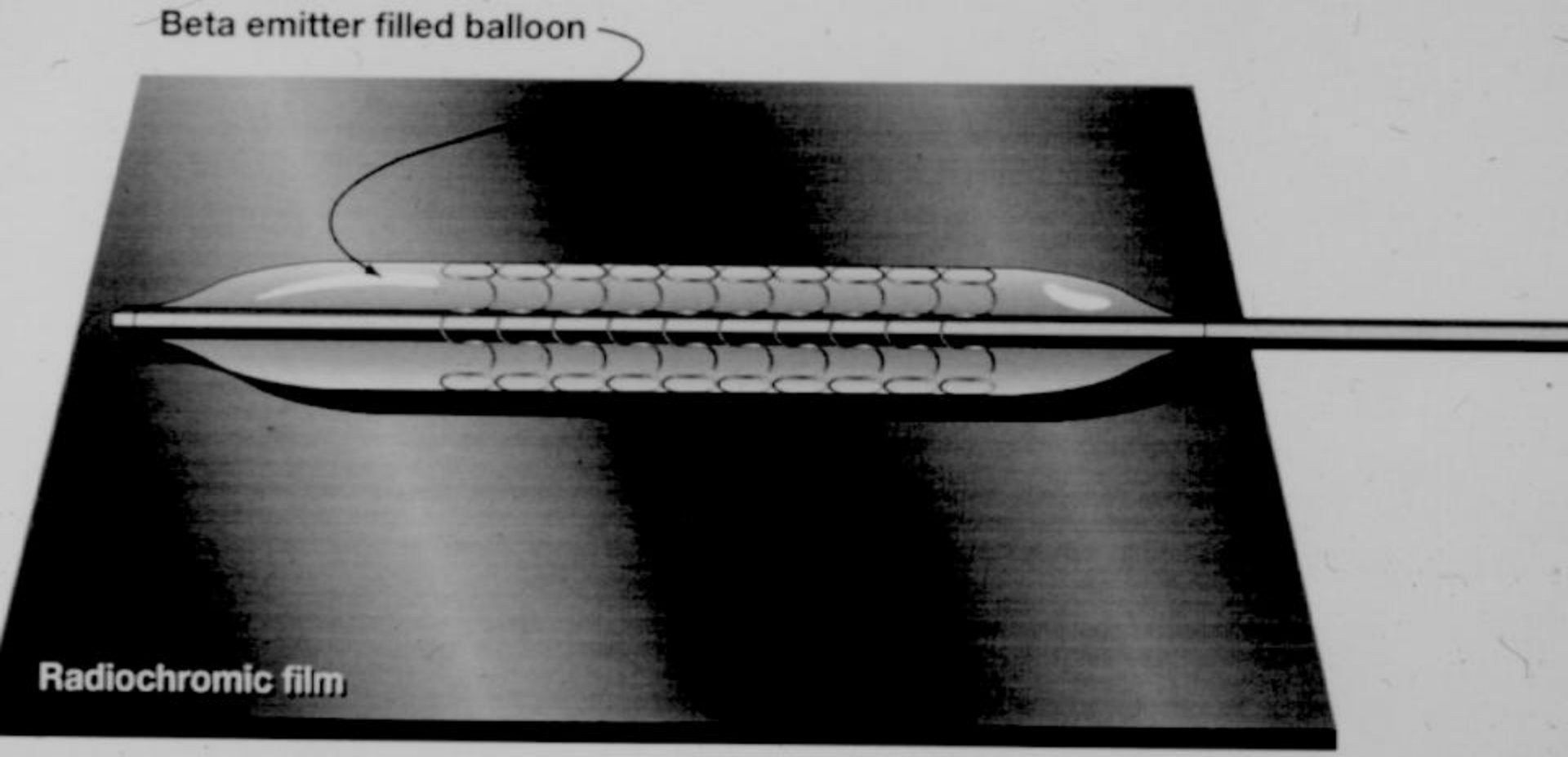
Our dosimetry approach

- Perform simultaneous IVUS and digital fluoroscopy to establish the true 3D anatomy of the artery and geometry of stent
- In each IVUS cut, find the stent struts in the image (struxels)
- Assign a strength to each struxel as

$$dS_i = S \frac{dp_i}{\sum_{\text{over all struxels, } j} dp_j}$$

Verification of the Dose Distributions

Verification would be by Radiochromic film and TLD


Beta emitter filled balloon
Radiochromic film

Progress Toward Dosimetry

In the first year of the project, we have:

- Established the infrastructure for the verification measurements.
- Begun the Monte Carlo calculations for the dose distributions for struxels.
- Begun the structure for the summation based on IVUS.